Dissertation of Doctor of Philosophy in
Brain and Cognitive Sciences

Predicting Psychosis Onset in Clinical-High Risk Individuals Using Functional Network Connectivity Biomarkers

기능적 뇌네트워크 간 연결성의 차이를 통한
임상적 고위험군에서 정신증 발병 예측

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Abstract

Among individuals at clinical high risk for psychosis (CHR) who show prodromal symptoms of psychosis, some progress to full-blown psychosis. There have been attempts to find markers predicting the onset of psychosis, and brain structures related to onset of psychosis have been reported. However, no studies have examined wide-range interactions at the functional network level that can adequately account for the schizophrenia, a dysconnectivity disorder.

To discover predicting markers for psychosis, I conducted a longitudinal study for a follow-up period of a minimum of 12 months. At the baseline, the resting-state functional magnetic resonance imaging was acquired from individuals at CHR (N = 69), individuals with first-episode psychosis (FEP) (N = 35), and healthy controls (HC) (N = 70). Eight psychosis-related functional networks were extracted, and interactions between paired functional networks were measured, resulting in estimations of 28 possible combinations. After the group comparison, correlation analyses between the altered network interactions and symptom severity were conducted to reveal clinical associations.

Seven of 69 (10%) individuals at CHR proceeded to full-blown psychosis (CHR-C). There were no significant difference in age, gender, and handedness among FEP, CHR-C, CHR-NC, and HC. Of the 28 combinations, there were

significant group differences in four functional network connectivity. The FEP group showed the

most severe degree of decrement in functional network connectivity compared to HC. Among all four significantly different functional network interactions, CHR-C showed no significant difference from FEP, while the nonconverters (CHR-NC) had significantly higher functional network connectivity compared to FEP. Among the altered combinations, the interaction between the anterior default mode network and salience network of the FEP group was associated with the overall negative psychotic symptom severity.

This is the first study to suggest that large network interactions can serve as potential markers of the psychosis onset by showing that the CHR-C is similar to FEP, while CHR-NC is comparable to HC. The degree of functional network connectivity in CHR may have prognostic implications regarding the risk of conversion to full-blown psychosis.

Keyword: Psychosis, functional MRI, Independent component analysis, Schizophrenia, Clinical-high risk for psychosis, Functional network connectivity

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Chapter 1. Introduction

Prodromal Symptoms of Psychosis

Patients with schizophrenia, a mental disorder that affects 1% of the world's population, show both positive (e.g., delusional thoughts and presence of hallucinations) and negative (e.g., avolition, apathy, difficulty in abstract thinking) symptoms[1]. Daily functioning of patients deteriorates due to these symptoms, which makes schizophrenia a very costly disease[2]. Schizophrenia is a neurodevelopmental disorder that progresses gradually, beginning with cognitive decline, mood problems social impairment, and functional decline during adolescence, followed by prodromal symptoms of psychosis, and then the onset of psychosis[3]. The neurodevelopmental hypothesis, which involves the influence of various factors including environmental and other developmental risk factors on the pathological processes, has been suggested to explain the pathological processes[4]. The neurodevelopmental hypothesis of schizophrenia has been further detailed by the 2-hit model, which suggests that two critical time points for the onset of psychosis exist[5]. According to the 2-hit model, problems in the early developmental period cause abnormalities in the brain network, and these problems appear as premorbid signs and symptoms in individuals who later develop schizophrenia. Then, at adolescent or early adulthood, a subtle decrease in neural plasticity and a loss of synapse result in attenuated psychotic symptoms.

Eighty to 90% of patients with schizophrenia have these prodromal symptoms prior to the onset of psychosis[6]. These facts imply that a critical period for early detection exists, which may help further improve prognosis and enhance the quality of life of patients with schizophrenia through early intervention[7]. In fact, there has been a movement toward explaining the pathophysiology of schizophrenia by investigating individuals with subthreshold symptoms, the individuals at clinical-high risk for psychosis (CHR).

CHR is defined as the presence of one or more of following: attenuated positive syndrome (APS), brief intermittent psychotic syndrome (BIPS), and genetic risk and deterioration in psychosocial functioning (GRD). Two of the three criteria focus on positive symptoms because positive symptoms of the prodromal phase, which appear later than negative symptoms, tend to be exacerbated and thus further lead to the onset of psychosis[8, 9]. Within two years, 20-35% of individuals at the prodromal phase progress to full blown psychosis[10]. Conversion rates showed a large variation between the different cohorts, and recently published studies tended to report smaller conversion rates[11-13]. This may be attributed to the appropriate management of the prodromal symptoms based on the accumulated understanding of CHR per se. In fact, meta-analysis studies reported that CHR individuals with appropriate intervention, such as psychological and/or antipsychotics treatment, have lower conversion rates to full-blown psychosis[10, 14]. Furthermore, there has been a movement towards understanding the progression

of psychosis and further finding early detecting biomarkers of psychosis through the investigation of these individuals[15]. In fact, research on CHR and Attenuated Psychosis Syndrome has been spotlighted, and Attenuated Psychosis Syndrome has been included in the recently revised DSM-5[16]. To acquire deeper insight into the pathophysiology of psychosis underlying the onset of psychosis and to further acquire clues for early detection of psychosis, magnetic resonance imaging (MRI) studies have been conducted with individuals at CHR[17-19].

Brain Abnormalities in Patients with Schizophrenia and in CHR

Brain abnormalities have been considered to be involved in the process of psychosis. In earlier MRI studies, researchers have focused on brain structural alterations to understand the pathophysiology of schizophrenia[20, 21]. Decreased volume in the temporal and frontal lobes, specifically in the superior temporal gyrus[21-23] and the anterior cingulate cortex[24, 25], respectively, has been reported to be involved in the onset of psychosis[26], and similar trends have also been observed in individuals at CHR[27-29]. More recently, the dysconnectivity hypothesis, suggesting that psychosis is caused by abnormal communications between brain regions, has been raised[30, 31]. This suggestion has been supported by MRI studies utilizing various modalities, such as diffusion tensor imaging and functional MRI[32, 33]. For instance, abnormalities in white matter fibers connecting the temporal lobe and the frontal lobe[34, 35], as well as aberrant functional

connectivity during mentalizing tasks, have been reported in patients with schizophrenia[36, 37]. The evidence supporting the dysconnectivity hypothesis is observed not only in patients with schizophrenia but also in individuals at CHR[32, 38]. In a previous study of CHR, authors have found that although CHR individuals showed sub-threshold symptom severity, functional connectivity was impaired in a manner similar to, but to a lesser degree than, that of patients with schizophrenia[38], and similar findings were confirmed by another CHR study[36]. Interestingly, both studies conducted with patients with schizophrenia and CHR reported that the fronto-temporal functional connectivity of patients with schizophrenia presented the greatest contrast to HC, while CHR showed a moderate degree of alteration.

While the majority of studies on psychosis have highlighted the abnormalities of the temporal and frontal lobes, some studies have provided evidence that other brain regions may be involved in psychosis[39, 40], highlighting the need of a more comprehensive approach. To approach brain research in a more comprehensive manner, not only the specific regions but also the functional networks consisting of temporally synchronized regions throughout the whole brain were studied. Functional networks have been identified in the human brain through several different approaches[41]. Among these approaches, the independent component analysis (ICA) has often been applied to explore the pathophysiology of psychosis at the functional network level[42-46]. ICA is a multivariate data-driven approach

that makes it possible to find shared features within the functional MRI data. It is thus non-biased and further allows us to discover more comprehensive aspects of functional connectivity by extracting functional networks[47, 48]. In addition to extracting functional networks, the ICA approach has an advantage of deriving various spectrums of signals, and the approach is an effective way for denoising confounding noise signals, such as motion and other physiological signals, hence enabling us to explore pure physiological features of the brain[49]. The relationship between functional networks and symptoms of schizophrenia have been investigated. The bilateral executive control networks (ECN), default mode network (DMN), dorsal attention network (DN), salience network (SN), auditory network (AN), and language network (LN) are indicated to be involved in the pathophysiology of schizophrenia[50-54]. The ECN is involved in working memory and is also known as the task-positive network[55]. The DMN plays a critical role in both social-related and self-related cognitive functions[56-59]. The SN is involved in detecting novel stimuli and switching from the default network to the attentional network[60, 61]. The DN functions as the top-down control center of voluntary attention and is thus involved in selective attention[62]. The AN is involved in auditory processing[63], and the LN is involved in language processing[64]. The disturbances in cognitive function or symptoms resulting from abnormalities in functional networks among patients with schizophrenia are parallel to the impairments in cognitions or symptoms that have been commonly reported among

patients with schizophrenia[65-67]. This pattern also appeared in CHR[68, 69], suggesting that a change at the functional network level exists even in individuals with subthreshold or brief psychotic symptoms, thus raising the possibility that investigating connectivity at the functional network level could enable us to obtain clues about psychosis progression.

Transition from Prodromal Symptoms to Full-blown Psychosis

To date, a number of possible markers that can predict the onset of psychosis have been discovered from MRI studies. Most of the studies were performed retrospectively, conducting MRI scans of the CHR individuals at the baseline and observing whether the onset of psychosis occurs during the follow-up period. According to MRI studies, structural differences in the superior temporal gyrus[29], insular cortex[70], parahippocampal gyrus[71], anterior cingulate cortex[72, 73], and hippocampus[74] may provide information about which of the individuals at CHR convert to full blown psychosis. A relatively fewer number of functional MRI studies have provided evidence of early detection markers predicting the onset of psychosis by emphasizing aberrant activations in various brain regions, including the prefrontal, brain stem, temporal, and parietal regions, that predated the onset of psychosis in CHR[75, 76]. In the study conducted by Allen and colleagues, connectivity between the prefrontal and brain stem regions predicted psychosis

onset, suggesting the possibility that predictive markers of psychosis can be found in terms of functional connectivity[75].

Often times, in order to measure the functional connectivity of the brain, functional MRI is obtained in the resting-state and further temporally analyzed to link regions that share information with each other[77]. The functional MRI obtained while individuals perform specific tasks tends to amplify the brain activation associated with the specific task, making it difficult to capture the condition of the rest of the brain. Meanwhile, acquiring functional MRI in the resting-state has the advantage of displaying the comprehensive brain physiology that is not associated with the task and rather further enables us to observe the submerged task-independent brain networks[78]. By better illustrating the association with the phenomenology of schizophrenia, resting-state studies help to better understand comprehensive aspects of schizophrenia[79]. Since resting-state studies enable us to observe the basic physiology of the brain, many studies have attempted to observe the functional connectivity of the individuals' mental illness utilizing this modality[80]. Through this approach, the impaired functional connectivity of schizophrenia has been observed, further confirming the dysconnectivity hypothesis to explain the pathophysiology of schizophrenia[81-83]. Extending the existing findings, further attempts have been made to find a psychosis onset prediction marker in terms of the resting-state functional network. In a multicenter follow-up study conducted by Anticevic and colleagues,

thalamocortical dysconnectivity of the CHR population was assessed at the baseline[84]. The authors reported that, at the baseline, individuals at CHR who eventually converted to full blown psychosis had thalamic hypoconnectivity with the prefrontal and cerebellar areas and hyperconnectivity between the thalamus and sensory motor areas.

Study Approach

Although MRI studies have contributed much to the clarification of the association between the brain and conversion to psychosis, there are additional features to consider. First, schizophrenia is a neurodevelopmental disorder, and a more sophisticated approach that can better describe the neurodevelopmental aspect of the disorder could thus elucidate markers predicting psychosis onset. During the brain developmental process, the interaction between functional networks plays important role[85]. Furthermore, genes associated with psychosis progression influence both synaptic plasticity and long-range connections[86]. These facts imply that when investigating predictive markers for schizophrenia, a neurodevelopmental disorder, the information regarding the interaction between a wide range of functional networks may be important. Secondly, because the symptoms of schizophrenia are complex, there is increasing evidence that psychotic symptoms can be better described in terms of interactions between functional networks[51, 87, 88]. In fact, the electrophysiological approaches, which are

influenced by interactions between various functional networks[89, 90], have provided evidence of markers predicting psychosis[91-93]. This emphasizes the importance of exploring predictive markers directly in terms of interaction between the functional networks.

To better elucidate potential markers predicting the onset of psychosis, I aimed to observe interactions between functional networks, which can provide a more comprehensive assessment of the neurodevelopmental progression of psychosis as well as the complex symptoms of schizophrenia. In order to directly observe the interaction between the functional networks, the functional network connectivity analysis was designed, which is an extended approach of the spatial ICA approach[94]. The functional network connectivity analysis estimates the association between functional networks, thus a more comprehensive view of brain physiology, which reflects synaptic plasticity, can be observed through larger-scaled distributed networks[95]. In fact, there is growing interest in how functional networks organically interact with each other as well as how this interaction is associated with an individual's cognitive processing[96]. I speculate that the complex association between psychotic symptoms and the brain can be better described by investigating functional network interactions rather than simply investigating at a single functional network level. Furthermore, the late developmental period of psychosis remains unclear but is suspected to be

associated with anomalies of synaptic plasticity[97]. Assessing the late developmental period of psychosis with functional network connectivity could help elucidate the predictive marker of schizophrenia.

The results regarding functional network connectivity should be interpreted with caution. While most structural MRI findings report brain volume reduction in patients with schizophrenia, functional network connectivity studies have reported contradicting findings, reporting both increased and decreased interactions between functional network connectivity in patients with schizophrenia. To prevent this confusion, I included schizophrenia patients in the current study to determine the influence of psychosis on functional network connectivity[94, 98]. A progressive brain change in patients with schizophrenia has been reported[99], so I concluded that this brain change could potentially interfere with the assessment of the pure influence of psychosis onset on functional network connectivity. Hence, I specifically included individuals with first-episode psychosis (FEP), who were diagnosed with brief psychotic disorder, schizophreniform disorder, schizophrenia or schizoaffective disorder within the past year[100]. Including the FEP group has the advantage of being able to exclude the possibility of brain change due to chronic illness, which enables to investigate pure aspects in the onset of psychosis.

Hypothesis

In the present study, I aimed to find a marker for predicting the onset of psychosis based on functional network connectivity. In order to do so, I explored the presence of psychosis onset longitudinally for at least one year after acquiring the baseline resting-state functional MRI of 69 individuals at CHR. After confirming the presence or absence of psychosis, I compared the differences in the baseline functional network connectivity between CHR who subsequently converted to full-blown psychosis (CHR-C) and CHR who did not convert to full-blown psychosis (CHR-NC). I hypothesized that whereas the functional network interaction among CHR-C be similar to that of FEP, the CHR-NC would be more similar to that of HC. Furthermore, I speculated that, if a significant group difference in functional network connectivity exists, the altered interaction between functional networks in the CHR and FEP groups would be associated with their symptom severity. Through this approach, I expected to specify which functional network interaction is associated with prodromal symptoms and early psychotic symptoms.

Chapter 2. Methods

Participants

Thirty-five individuals with FEP, sixty-nine individuals at CHR and, seventy demographically matched HC were selected from the subject pool of the study cohorts (from April 2010 to March 2017). The cohorts were recruited for a longitudinal project to investigate individuals at high risk of developing psychosis either from out-patient clinic of Seoul National University Hospital or from the Seoul Youth Clinic, Seoul, Republic of Korea[101, 102]. The participants initially contacted the Seoul Youth Clinic via the website, telephone or referral from local clinics.

All participants were assessed with the Structured Clinical Interview for DSM-IV (SCID) Axis I[100]. In accordance with the DSM-IV criteria[100], participants who were recently (i.e., within 1 year) diagnosed with the following psychotic

disorders were included in the FEP group: brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. The mental status of individuals was confirmed by experienced psychiatrists. Upon including participants in the cohorts, the Korean version of the Wechsler Adult Intelligence Scale[103] was administered to all participants to assess their intelligence quotient (IQ). Individuals with intellectual disability (IQ below 70) were not included in the cohorts.

The individuals satisfying the criteria of the Structured Interview for Prodromal Symptoms (SIPS)[9] were included in the CHR group. Specifically, CHR was defined as those who satisfy the criteria for at least one of the prodromal states of psychosis: APS, BIPS, and/or GRD. APS was defined as the presence of any positive items on the Scale of Prodromal Symptoms (SOPS) (Table 1)[104] in the prodromal range, with symptoms occurrence during the past year, or showing attenuated psychotic symptoms upon at least one point during the past year and exhibiting these symptoms at one or more occasions per week for the past month. BIPS subjects showed at least one symptom from the positive criteria on the SOPS scale in the psychotic range, with symptoms beginning within the past 3 months and the presence of the symptoms several minutes a day for at least once per month. GRD subjects showed significantly declined functioning, with at least a 30% decrease in the Global Assessment of Functioning (GAF) scale[105] over the past year, and had a genetic risk due to a first-degree relative with any psychotic

disorder or schizotypal personality disorder[106]. The exclusion criteria for the CHR were: diagnosis of a psychotic disorder in the past; antipsychotic use; history of substance abuse or dependence; significant head trauma or neurological disease; cognitive sequelae due to medical problems; sensory impairments. For at least 1 year after MRI scanning, all CHR participants were followed regularly to identify whether they converted to full-blown psychosis.

HC participants were recruited from internet advertisements. All HC participants were assessed and confirmed according to the SCID Non-patient Edition[100]. The participants were excluded if they had any history of a psychiatric disorder, neurological illness, substance abuse, or considerable head injury; any first- to third-degree biological relatives diagnosed with a psychiatric disorder; or evidence of a medical disease with documented cognitive decline.

The present study was performed in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board of Seoul National University Hospital. After providing a complete description of the study to the participant, written informed consent was obtained from each participant before they were included in the study. For individuals younger than the age of 18, written informed consent was obtained from both the participants themselves and their caretakers or guardians.

Clinical measures and Follow-up

The Positive and Negative Syndrome Scale (PANSS) (Table 2)[107] was administered to all participants in FEP group to assess their symptom severity. The symptom severity of all participants in CHR group were assessed according to the SOPS. The general functional status of all participants in psychosis spectrum groups were assessed with GAF[105]. In CHR participants, clinical follow-up occurred for a period of average 54.4 ± 23.0 months, ranging from 12.3 to 87.0 months, after their baseline MRI scans.

Data Acquisition

Functional and structural images were obtained with a Siemens 3T Trio MRI scanner (Siemens Magnetom Trio, Erlangen, Germany) using a 12-channel head coil. The T1-weighted anatomical image was acquired using magnetization prepared rapid gradient echo (echo time [TE] / repetition time [TR] = 1.89 / 1670 ms, field of view [FOV] = 250 mm, flip angle = 9°, matrix = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm^3, 208 slices). For each subject, we collected a rest scan comprising 116 contiguous echo-planar imaging (EPI) functional images (TE / TR = 30 / 3500 ms, FOV = 240 mm, flip angle = 90°, matrix = 128 × 128, voxel size = 1.9 × 1.9 × 3.5 mm^3, 35 slices). To limit possible head movements and subsequent motion artifacts, head cushions were used. During resting-state image acquisition, the participants were instructed to relax with their eyes closed and the participants were asked to move as little as possible.

Data Preprocessing

The first 4 volume images of rest scan were discarded, and the remaining 112 functional images were preprocessed using the Statistical Parametric Mapping software package, version 12 (SPM12; www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, London, UK). Firstly, functional images were processed by slice timing correction and subsequently realigned to correct for head motions. None of the scans exceeded the head motion criteria (translation > 2.5 mm and rotation > 2.5° in any directions). After the realignment, functional volumes were co-registered on each participant's structural volume. The image was segmented into gray matter, white matter, and cerebrospinal fluid, and was spatially normalized to the standardized space of the Montreal Neurology Institute (MNI) (http://www.mni.mcgill.ca/). The normalized functional volume was resampled to a voxel size of 3 × 3 × 3 mm^3 and spatially smoothed with 6 × 6 × 6 mm^3 full width at half maximum (FWHM) isotropic Gaussian kernel.

Functional Network Extraction

The temporally distinct resting-state components were extracted from the preprocessed functional data utilizing the GIFT group ICA Toolbox (version 3.0a; http://mialab.mrn.org/software/gift/). Twenty-one spatially independent components were extracted according to the minimum description length

criteria[108]. Each participant's functional data was initially reduced using principal component analysis. Then, independent component estimation was performed using the Infomax algorithm[109], and the procedure was repeated 20 times in ICASSO for the stability of the decomposition[110]. After the decomposition, centrotype of each functional networks were calculated to estimate the robustness of each functional networks (Fig. 1). A complete description of the components extraction can be found in Calhoun *et al.*[111].

To validate that the extracted functional networks corresponds with other functional networks, each extracted mean functional network maps was compared with previously reported functional networks[41, 112, 113]. The functional components of the present study and predefined functional networks were compared by Pearson's correlation between vectorized images based on with spatial cross-correlation analysis. If the correlation coefficient values from the Pearson's correlation analysis was above $R > 0.25$, it was considered as highly coherent[114]. After determining bilateral ECN, both anterior and posterior DMN, DN, SN, AN, and LN were according to independently defined atlases[41, 112, 113] functional networks were visually inspected and confirmed.

Functional Network Connectivity Analysis

Using the FNC Toolbox[94], ICA time courses data was band-passed filtered with a Butterworth filter at cutoff frequencies of 0.007 to 0.14 Hz. Maximal-lagged

correlation (−7 to +7 seconds) was examined between the pair of the selected functional networks using following equations:

$$\rho_{i_0+\Delta i} = \frac{\left(\bar{X}_{i_0}^T\right)\left(\bar{Y}_{i_0+\Delta i}^T\right)}{\sqrt{\bar{X}_{i_0}^T \bar{X}_{i_0}} \times \sqrt{\bar{Y}_{i_0+\Delta i}^T \bar{Y}_{i_0+\Delta i}}}$$

ρ is the correlation value and calculated between time courses $\bar{X}$ and $\bar{Y}$; i_0 is the starting reference; and Δi is change in time (in seconds) which was set at -7 to +7 for the present study.

For the functional network connectivity analysis, 8 functional networks were paired to each other. Thus,

$$\frac{8!}{2! \times (8-2)!} = 28$$

28 different combinations of functional network interactions were extracted per participant. The results were Fisher's transformed to a *Z*-score for the further statistical analysis.

Statistical Analysis

The group effects of the functional network connectivity were assessed with one-way analysis of variance (ANOVA) and to correct for the multiple

comparisons, the significance level was set at the Bonferroni corrected p values (0.05 / 28). For the post-hoc group comparison, the Bonferroni post hoc test was applied. To find the association between altered functional network connectivity and symptom severity, Spearman's correlation analysis was used. During the Spearman's correlation analysis, functional network connectivity values of individuals in each group were Fisher's transformed to Z-scores, and any value deviating more than 1.96 from the mean value ($Z = 0$) was considered to be an outlier and was excluded from the analysis. The significance level was thresholded at 0.05 for all statistical analyses, and the Statistical Package for the Social Sciences (SPSS) for Windows, version 23.0 (SPSS Inc., Chicago, IL, USA) was used for statistical tests.

Chapter 3. Results

Demographic Clinical Data

Among the 69 participants in the CHR group, 7 participants made the transition to the full-blown psychosis (10%). There were no significant differences in demographic characteristic, such as age, gender, or, handedness, among CHR-C, CHR-NC, FEP, and HC. At the baseline, there was no significant difference between CHR-C and CHR-NC in all domains as well as overall prodromal symptom severity assessed with SOPS. The demographical and clinical characteristics are summarized in Table 3.

Functional Network Extraction and Comparison with other Functional Networks

Among the 21 spatially independent components (Fig. 2), 8 psychosis related functional networks were chosen for further analysis. Each functional network

was compared with predefined functional networks[41, 112, 113], and the correlation coefficients with the best corresponding predefined functional networks were as follows (Fig. 3): $R = 0.38$ for dorsal DMN[112] and anterior DMN (Table 4), $R = 0.58$ for ventral DMN[112] and posterior DMN (Table 5), $R = 0.58$ for superior parietal lobule[113] and DN (Table 6), $R = 0.32$ for language network[112] and LN (Table 7), $R = 0.65$ for left frontoparietal[41] and left ECN (Table 8), $R = 0.57$ for right frontoparietal[41] and right ECN (Table 9), $R = 0.63$ for auditory network[41] and AN (Table 10), and $R = 0.38$ for bilateral anterior insula[113] and SN (Table 11).

Resting-State Functional Network Connectivity

Among 28 possible combinations, correlation coefficient values of 4 functional network connectivity demonstrated significant group difference by one-way ANOVA at the significance level of Bonferroni corrected *p*-value = (0.05 / 28) (Fig. 4). The significantly different pairs include: anterior DMN – SN; anterior DMN – AN; DN – AN; LN - AN (Fig. 5). Compared to HC, the FEP group had significantly reduced functional network connectivity in all of the aforementioned pairs. While HC and CHR-NC had significantly enhanced functional network connectivity, the functional network connectivity of the CHR-C group did not show a significant difference compared to FEP.

Correlation of Functional Network Connectivity and Clinical Symptoms

In the FEP group, the functional network connection between the anterior DMN and the SN was negatively correlated with overall negative symptom severity as assessed by the PANSS (R = -0.476, p = 0.004) (Fig. 6).

Chapter 4. Discussion

Summary

Based on the dysconnectivity hypothesis, schizophrenia is a disorder caused by abnormal wiring between brain regions[81, 83, 115]. To date, the change in interactions between various functional networks in CHR, as well as whether the change predates progression to full-blown psychosis, has not been elucidated. In the present study, the interaction abnormality among various functional networks, including anterior DMN, SN, LN, AN, and DN, showed the greatest decrements in FEP, and while CHR-C showed changes similar to FEP, the CHR-NC group showed a lesser degree of change which was similar to that of HC. This implies that abnormal interactions between functional networks predate full blown psychosis onset and that the functional network connectivity could thus serve as a biomarker to predict the progression to full-blown psychosis. To my knowledge,

this is the first resting-state functional MRI study to be conducted in a single center and demonstrate baseline functional connectivity differences between CHR-C and CHR-NC. I was able to reveal biomarkers through a relatively small number of participants compared to a multi-center study by applying a sensitive approach that embraces interactions among more diverse brain regions.

Group Differences in Functional Network Connectivity

In a previous study conducted with schizophrenia and their first-degree relatives, the functional network connectivity of schizophrenia patients was significantly reduced compared to that of HC, and the functional network connectivity of the patients' first-degree relatives was in between that of schizophrenia patients and healthy controls, with no significant difference compared to HC[98]. In addition, as in a past functional connectivity study of CHR and FEP, I expected that CHR would show moderately altered functional connectivity compared to that of the FEP group[38]. Other previous neuroimaging studies on CHR have shown that brain imaging findings of CHR were similar to those of individuals with established psychotic symptoms, except that the degree of alteration was less severe[10, 36, 116].

Before I proceeded with this study, I anticipated that the both CHR-C and CHR-NC would have a pattern similar to that of the first-degree relative populations of the previous study[98]. Of the 28 possible combinations of functional

network connectivity, 4 combinations showed significant group differences at a strict level of Bonferroni corrected *p*-value ($p < 0.05/28$). As we predicted, FEP showed significantly decreased functional network connectivity compared to HC in all combinations. In 4 combinations in which FEP presented significant alterations, both CHR-C and CHR-NC showed no significant difference compared to HC. However, while all combinations of CHR-NC was significantly higher than that of FEP, combinations of CHR-C showed no significant difference from FEP. All of the significantly aberrant functional network interactions of the present study are in line with previous findings. Elaborating on previous studies linking the onset of psychosis trajectory to brain imaging, present findings may serve as an additional reference by taking a more comprehensive perspective of the brain functional networks.

Psychosis and Auditory Network Impairment

The AN was found to be involved in three of the four altered functional network interactions. The AN mainly consists of the temporal region, of which the superior temporal gyrus constitutes the largest portion (Table 10). Previously, many studies have reported that the superior temporal gyrus is a core region associated with psychosis[20, 117-119]. The decline in functioning with regards to language and working memory in schizophrenia was reported to be associated with abnormal functioning within the superior temporal gyrus[36, 37], and present

results are in close accordance with these previous findings. Specifically, the AN had decreased interactions with i) LN; ii) anterior DMN; and iii) DN.

The extracted LN in this study included both the Broca's area and Wernicke's area and tended to be lateralized to the left hemisphere (Table 7). The impairment of language processing in patients with schizophrenia has been reported[120], and this idea was further proven through MRI studies showing that brain abnormalities within LN are associated with the aberrant language functioning[64, 121]. A previous schizophrenia study reported a decrease in connectivity between these two networks[122], and a pattern similar to present results was observed. The decreased interaction between these two networks that was observed in both studies may be related to the problem of language processing. However, these results should be interpreted with caution, since both results had limitations with regards to associating imaging findings with the individuals' language performance. Utilizing task functional MRI to directly demonstrate how interactions between these two networks are related to language processing would be an interesting topic for future research.

The extracted anterior DMN in this study included the medial prefrontal cortex (Table 4). Thus, the results replicate the results of previous studies reporting fronto-temporal dysconnectivity[30, 123-127] and further extent the dysconnectivity findings at the functional network level. Fronto-temporal dysconnectivity is reported to be an important pathway that causes psychotic features, such as

hallucination[35]. The present results, which show decreased connectivity of the anterior DMN and AN, mainly composed of the prefrontal and temporal regions, respectively, suggest that the consistently reported fronto-temporal dysconnectivity may be due to a more complex underlying mechanism. At the functional network level, the anterior DMN is reported to be associated with self-oriented thinking[128-131]. The core pathophysiology of schizophrenia is described as not being able to distinguish between self-oriented thoughts and external stimuli[132], and it is interesting to note that a reduced association between anterior DMN, which is involved in self-thinking, and AN, an external auditory stimulus related functional network, was found in present study.

The extracted DN in this study included the parietal area and the medial prefrontal area (Table 6). The DN plays an important role in filtering non-important stimuli through top-down processing[133]. In schizophrenia patients, the top-down processing impairment has been reported to be associated with psychotic symptoms[134, 135]. I contemplate that the decreased interaction between the DN and the AN led to an inability to suppress the irrelevant external stimuli. The abnormal interaction between DN and AN has been reported to be associated with another psychosis predicting marker, the mismatch negativity[136, 137]. It would be an intriguing research topic to find a direct association between mismatch negativity and the functional connectivity network between DN and AN. Interestingly, brain regions associated with both the DN and the AN are reported

to be the brain regions where complete maturation occurs at the latest[138, 139]. This implies that if we can detect these risk factors early enough to intervene appropriately, there is a possibility that the abnormal brain maturation can be corrected to some degree, which could lead to preventing the onset of psychosis. A longitudinal study that reveals the relationship between changes in functional network connectivity by applying the appropriate intervention to individuals in the high-risk group would help address this possibility.

Psychosis and Interaction between Anterior DMN and SN

The interaction between the anterior DMN and the SN also showed a significant group difference, with a reduced functional network connectivity in the FEP group. Similar to other interactions, while the functional network connectivity of the CHR-C were similar to that of the FEP, the connectivity of the CHR-NC were similar to that of the HC. Although the finding was not statistically significant, the mean correlation coefficient of functional network connectivity between the anterior DMN and the SN of CHR-NC group was mildly elevated, compared to HC. When a stimulus is presented, our brain switches from the task-negative mode to the task-positive mode, during which the dominance switches from the DMN to the ECN[140-142]. The SN is reported to play a critical role in switching from DMN to ECN[60, 143-145]. A poor interaction between the DMN and the ECN, which is viewed as an inability to balance self-monitoring and task

performances, was reported in schizophrenia studies[146, 147]. I speculate that an enhanced interaction between the anterior DMN and the SN could help prevent the onset of psychosis. However, if these interactions are not well enhanced, then individuals at CHR may proceed to full-blown psychosis.

An association between altered functional network connectivity and psychotic symptom severity was observed in the FEP group. The reduction of functional network connectivity between the anterior DMN and SN was negatively correlated with the overall negative symptom severity measured by PANSS (Fig. 6). As the SN acts as a switch network that induces the shift from a task-negative mode to a task-positive mode[60, 145, 148], a task may involve a two-step process in which the SN first intervenes in the task-negative state and then triggers the switch to the task-positive state. A past study reported the association between the severity of negative symptoms of patients with schizophrenia during remission and the interaction between SN and ECN[149]. Taking into consideration both this previous finding as well as present results, I concluded that different functional network interactions, the DMN - SN and the SN – ECN, distinctively affect negative symptoms of patients with schizophrenia during FEP and during remission, respectively. Hence, as the first step, the DMN – SN influences negative symptoms immediately after the onset of psychosis, and then, as the second step, the SN – ECN influences negative symptoms during the remission state. This fact implies that interactions of SN with DMN and ECN can be

explicit markers of the specific psychosis state. Based on the results of this study and the previous study[149], it would be interesting to explore how patterns of interactions between SN and the two distinctive functional networks, the DMN and the ECN, change from FEP to the psychotic remission state in follow-up studies. There was no significant association between prodromal symptom severity assessed with SOPS and the interaction between anterior DMN and LN. I hypothesize that the mild nature of the deterioration in functional network connectivity and/or symptomatic behavior of the CHR group may have hindered revealing the association between the two elements. I speculate that such association in the CHR group can be better determined in follow-up studies in which information about the trajectory of both functional networks and prodromal symptoms can be acquired.

Limitations

The present study yields some limitations. I attempted to completely match the demographic data of the participants of all groups included in this study, but the IQ was not matched. The IQ itself is an index that reflects the pathophysiology of psychosis, so it was difficult to match the IQ among the 3 groups[150]. In addition, I did not include IQ as a covariate in the statistical analysis because the inclusion of IQ as a covariate could dilute the influence of pathophysiology on the functional network connectivity findings. The main focus of the present study was to explore

the transition to psychosis in CHR. The post-hoc analyses revealed no significant difference in IQ between CHR-NC and CHR-C, CHR-NC and HC, and CHR-C and HC. Secondly, limitations could exist with regards to the relatively small number of CHR-C group included in the study. In addition, the transition rate to full-blown psychosis from CHR was relatively lower than that of other centers, leading to only a limited number of participants in the CHR-C group. An additional increase in the CHR-C ratio can be observed with longer follow-up periods. However, according to previous literature, the conversion rate was highest in the first year and then decreased sharply thereafter[151]. Thus, similar to other studies, I concluded that a 1 year follow-up period would be sufficient[152, 153]. Despite this disadvantage, present study had the strength of having relatively fewer confounding factors because the data were acquired from a single center. For example, all MRI data were acquired from the same MRI machine using the same protocol, and participants taking antipsychotics at the baseline were not included due to the cohort's CHR enrollment criteria. Furthermore, including a small number of participants in an imaging study does not raise the false positive rate and rather decreases the sensitivity[154]. Hence, the significant functional network connectivity derived from the present study can be interpreted as a meaningful result. However, readers need to take into consideration the potential false negative findings induced by the relatively small number of participants.

Chapter 5. Conclusion

This study provides evidence that changes in functional network connectivity may be present in individuals at CHR who only have subthreshold symptoms but later convert to full-blown psychosis. The fact implies that the disturbance of functional network connectivity may predispose psychosis onset and thus be used as neural markers for psychosis onset. In previous MRI studies, potential biomarkers were primarily focused on prefrontal and temporal regions. However, I observed evidence that abnormal interactions of five functional networks, including anterior DMN, AN, SN, LN, and DN, may serve as candidate markers. Current functional networks consisted of not only prefrontal and temporal regions but also relatively overlooked areas, such as the parietal region. This means that more diverse regions of the brain can be used as neural markers and that there is a possibility of finding more sensitive markers through a comprehensive

investigation of various parts of the brain. Early detection through predictive markers, followed by appropriate intervention, may contribute to better prognosis and quality of life of patients with schizophrenia, and I expect my findings to serve as a cornerstone in such process.

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Tables

Table 1. Structure of the Scale of Prodromal Symptoms and measured symptoms[104]

Positive Symptoms
Unusual Thought Content/Delusional Ideas
Suspiciousness/Persecutory Ideas
Grandiosity
Perceptual Abnormalities/Hallucinations
Disorganized Communication
Negative Symptoms
Social Anhedonia
Avolition
Expression of Emotion
Experience of Emotions and Self
Ideational Richness
Occupational Functioning
Disorganization Symptoms
Odd Behavior and Appearance
Bizarre Thinking
Trouble With Focus and Attention
Personal Hygiene
General Symptoms
Sleep Disturbance
Dysphoric Mood
Motor Disturbances
Impaired Tolerance to Normal Stress

Table 2. Structure of the Positive and Negative Syndrome Scale and measured symptoms[107]

Positive Scale
Delusions
Conceptual disorganization
Hallucinatory behavior
Excitement
Grandiosity
Suspiciousness
Hostility
Negative Scale
Blunted affect
Emotional withdrawal
Poor rapport
Passive-apathetic social withdrawal
Difficulty in abstract thinking
Lack of spontaneity & flow of conversation
Stereotyped thinking
General Psychopathology Scale
Somatic concern
Anxiety
Guilt feelings
Tension
Mannerisms & posturing
Depression
Motor retardation
UncooperatJveness
Unusual thought content
Disorientation
Poor attention
Lack of judgment & insight
Disturbance of volition
Poor impulse control
Preoccupation
Active social avoidance

Table 3. Demographic and clinical characteristics of the participants

	FEP (*N*=35)		CHR-C (*N*=7)		CHR-NC (*N*=62)		HC (*N*=70)		Statistics	
	Mean	SD	Mean	SD			Mean	SD		
Age (year)	22.40	5.32	23.57	4.61	20.92	3.81	22.31	4.04	1.826	0.144
Gender (M / F)	16 / 19		5 / 2		43 / 19		40 / 30		5.841	0.120
Handedness (R / L)	30 / 5		5 / 2		58 / 4		65 / 5		5.146	0.161
Estimated IQ	97.66	13.61	105.86	8.59	107.90	12.76	109.63	12.25	7.439	< 0.001
Clinical rating scales	Mean	SD	Mean	SD					*F / T*	*p*
PANSS										
Total	67.20	12.61								
Positive	15.91	4.86								
Negative	17.03	4.86								
General	34.26	6.89								
SOPS										
Total			34.00	8.45	33.92	12.02			-0.017	0.986
Positive			10.71	1.89	10.03	4.00			-0.443	0.659
Negative			13.14	4.30	13.18	6.57			0.014	0.989
Disorganization			5.29	3.15	3.74	2.59			-1.463	0.148
General			4.86	3.48	6.97	4.18			1.283	0.204
GAF	47.17	10.06	52.29	4.64	52.94	9.36			4.285	0.016

Notes: SCZ, schizophrenia; CHR-C, clinical-high risk converter; CHR-NC, clinical-high risk nonconverter; HC, healthy control; IQ, Intelligence quotient; PANSS, Positive and Negative Syndrome Scale; SOPS, Scale of Prodromal Symptoms Scores; GAF, Global Assessment of Functioning

Table 4. Anatomical description of the anterior default mode network. Voxels above the threshold of Z > 2 within converted Z map of each component are presented. Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html). na: no strong (Z > 2) contribution of the component.

Anterior Default Mode Network

Area	Brodmann Area	volume (cc) left / right hemispheres	random effects: Max Value (x, y, z) left / right hemispheres
Medial Frontal Gyrus	9, 10, 11, 25, 32	11.3/10.3	8.9 (-3, 55, 0)/7.7 (3, 55, 0)
Anterior Cingulate	10, 24, 25, 32, 33	7.4/6.5	7.2 (-3, 47, -2)/6.5 (3, 47, -2)
Extra-Nuclear	*	0.2/0.3	2.2 (-3, 29, 4)/2.6 (3, 27, 12)
Superior Frontal Gyrus	8, 9, 10	9.2/4.6	4.4 (-9, 64, 8)/4.0 (3, 56, 22)
Posterior Cingulate	23, 29, 30, 31	2.8/1.6	3.6 (0, -48, 25)/3.4 (3, -48, 22)
Cingulate Gyrus	23, 24, 31, 32	3.9/3.5	3.4 (0, -51, 27)/3.4 (3, 30, 26)
Precuneus	7, 19, 31	1.5/0.5	3.2 (0, -48, 30)/2.8 (3, -51, 30)
Rectal Gyrus	11	0.4/0.3	3.1 (-3, 31, -19)/2.7 (3, 31, -19)
Subcallosal Gyrus	25, 34	0.4/0.1	3.0 (-3, 23, -11)/2.7 (3, 23, -11)
Superior Temporal Gyrus	38	1.7/0.7	3.0 (-33, 10, -23)/2.7 (30, 13, -23)
Middle Frontal Gyrus	8, 9, 10	1.0/na	3.0 (-21, 64, 8)/na
Inferior Frontal Gyrus	47	0.6/0.4	2.8 (-39, 17, -16)/2.4 (30, 16, -21)
Orbital Gyrus	11	0.1/0.1	2.6 (-3, 43, -20)/2.3 (3, 43, -20)
Uncus	28, 34	0.3/0.1	2.5 (-18, 2, -20)/2.0 (21, 2, -20)
Parahippocampal Gyrus	34	0.3/0.1	2.5 (-15, 2, -18)/2.3 (18, -1, -18)

Table 4. (continued)

Inferior Parietal Lobule	39	0.3/na	2.3 (-45, -68, 39)/na
Caudate	*	0.1/0.1	2.2 (-6, 11, -6)/2.3 (6, 8, -5)
Angular Gyrus	39	0.3/na	2.1 (-48, -68, 37)/na

Table 5. Anatomical description of the posterior default mode network. Voxels above the threshold of Z > 2 within converted Z map of each component are presented. Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html). na: no strong (Z > 2) contribution of the component.

Posterior Default Mode Network

Area	Brodmann Area	volume (cc) left / right hemispheres	random effects: Max Value (x, y, z) left / right hemispheres
Precuneus	7, 19, 23, 31, 39	19.3/18.9	9.9 (0, -71, 45)/9.7 (3, -71, 42)
Superior Parietal Lobule	7	1.5/0.6	8.5 (-3, -64, 56)/6.4 (6, -64, 53)
Cuneus	7, 19	1.2/1.0	5.9 (0, -68, 31)/6.0 (3, -65, 31)
Cingulate Gyrus	23, 31	3.3/2.7	4.5 (0, -60, 28)/4.5 (3, -48, 38)
Extra-Nuclear	*	0.5/1.0	3.5 (-3, -40, 8)/3.8 (6, -40, 8)
Paracentral Lobule	5	0.6/0.5	3.6 (0, -41, 52)/3.8 (3, -41, 49)
Postcentral Gyrus	7	0.3/0.2	3.8 (-6, -52, 63)/3.0 (6, -49, 66)
Posterior Cingulate	23, 29, 30, 31	2.2/3.8	3.2 (-3, -60, 25)/3.8 (3, -40, 24)
Sub-Gyral	*	0.9/1.3	3.3 (-15, -57, 22)/3.6 (18, -57, 25)
Parahippocampal Gyrus	34	na/0.2	na/3.0 (9, -41, 5)
Inferior Parietal Lobule	7, 39	0.2/0.4	2.4 (-42, -68, 39)/2.8 (42, -68, 39)
Angular Gyrus	39	0.3/0.3	2.4 (-39, -74, 31)/2.2 (45, -65, 34)
Superior Temporal Gyrus	22, 38	na/0.3	na/2.3 (59, -49, 19)
Superior Occipital Gyrus	19	0.1/na	2.2 (-36, -77, 31)/na
Supramarginal Gyrus	40	na/0.1	na/2.1 (56, -48, 22)

Table 6. Anatomical description of the dorsal attention network. Voxels above the threshold of Z > 2 within converted Z map of each component are presented. Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html). na: no strong (Z > 2) contribution of the component.

Dorsal Attention Network			
Area	Brodmann Area	volume (cc) left / right hemispheres	random effects: Max Value (x, y, z) left / right hemispheres
Medial Frontal Gyrus	6, 32	4.0/5.5	6.5 (-3, -8, 67)/7.1 (3, -8, 67)
Precentral Gyrus	4, 6	4.6/5.6	5.5 (-24, -23, 67)/6.6 (27, -20, 67)
Postcentral Gyrus	2, 3, 4, 5, 7	4.2/4.9	6.6 (-3, -43, 66)/6.2 (6, -43, 66)
Superior Frontal Gyrus	6	2.0/2.3	5.4 (-3, -3, 66)/5.9 (6, -5, 67)
Paracentral Lobule	4, 5, 6, 31	4.9/4.3	5.8 (-3, -38, 65)/6.0 (3, -35, 65)
Cingulate Gyrus	24, 31, 32	1.3/1.9	3.9 (0, -3, 47)/4.2 (3, -6, 47)
Precuneus	7	0.9/1.3	3.4 (-3, -49, 61)/4.1 (3, -52, 61)
Sub-Gyral	40	1.3/1.1	3.4 (-9, -38, 60)/3.1 (12, -44, 60)
Superior Parietal Lobule	5	na/0.1	na/2.4 (21, -41, 60)

Table 7. Anatomical description of the language network. Voxels above the threshold of Z > 2 within converted Z map of each component are presented. Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html). na: no strong (Z > 2) contribution of the component.

Language Network

Area	Brodmann Area	volume (cc) left / right hemispheres	random effects: Max Value (x, y, z) left / right hemispheres
Superior Temporal Gyrus	13, 21, 22, 38, 39, 42	11.7/8.9	5.0 (-53, -57, 25)/5.3 (59, -49, 19)
Supramarginal Gyrus	40	4.9/3.8	5.1 (-56, -54, 25)/5.1 (59, -46, 22)
Middle Temporal Gyrus	19, 21, 22, 39	12.8/9.0	4.2 (-62, -35, 2)/5.0 (59, -38, 5)
Inferior Frontal Gyrus	45, 46, 47	6.9/1.7	5.0 (-50, 20, -9)/3.1 (50, 23, -11)
Medial Frontal Gyrus	6, 8, 9, 10, 11	3.2/3.4	4.6 (-3, 53, 19)/4.8 (3, 54, 25)
Superior Frontal Gyrus	6, 8, 9, 10	7.8/8.3	4.7 (-3, 56, 22)/4.7 (3, 56, 22)
Inferior Parietal Lobule	40	0.9/1.6	3.1 (-62, -42, 24)/4.5 (59, -42, 24)
Angular Gyrus	39	0.7/na	3.6 (-50, -60, 31)/na
Sub-Gyral	*	0.2/0.7	2.6 (-50, -21, -9)/3.6 (48, -29, -1)
Middle Frontal Gyrus	6, 8, 47	2.2/0.4	3.3 (-45, 11, 46)/2.2 (48, 11, 44)
Insula	13	na/0.3	na/2.8 (50, -40, 19)
Precuneus	7, 31	1.3/0.6	2.7 (0, -54, 36)/2.5 (3, -53, 39)
Cingulate Gyrus	31	0.2/na	2.6 (-3, -48, 38)/na
Inferior Temporal Gyrus	21	0.3/0.1	2.6 (-56, -7, -15)/2.6 (59, -7, -15)
Caudate	*	0.1/0.1	2.5 (-6, 3, 8)/2.2 (6, 3, 8)
Precentral Gyrus	9	0.1/na	2.0 (-45, 22, 35)/na

Table 7. (continued)

Orbital Gyrus	11	0.1/na	2.0 (-3, 49, -20)/na

Table 8. Anatomical description of the left executive control network. Voxels above the threshold of Z > 2 within converted Z map of each component are presented. Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html). na: no strong (Z > 2) contribution of the component.

Left Executive Control Network

Area	Brodmann Area	volume (cc) left / right hemispheres	random effects: Max Value (x, y, z) left / right hemispheres
Superior Parietal Lobule	7	4.6/0.6	8.9 (-33, -67, 50)/2.7 (36, -65, 50)
Inferior Parietal Lobule	7, 39, 40	11.8/0.1	7.5 (-39, -65, 47)/2.3 (39, -65, 47)
Precuneus	7, 19, 39	4.2/na	6.5 (-24, -70, 50)/na
Middle Frontal Gyrus	6, 8, 9, 10, 11, 46	24.7/na	6.4 (-50, 19, 29)/na
Inferior Frontal Gyrus	9, 10, 44, 45, 46, 47	14.5/na	6.2 (-45, 44, -2)/na
Sub-Gyral	*	3.1/na	5.0 (-42, 41, -2)/na
Precentral Gyrus	9, 44	0.8/na	4.5 (-45, 19, 35)/na
Superior Frontal Gyrus	6, 8, 9, 10	5.3/na	4.4 (-36, 58, -3)/na
Superior Temporal Gyrus	22, 38	1.2/na	4.1 (-50, 17, -8)/na
Angular Gyrus	39	2.3/na	3.6 (-45, -65, 36)/na
Medial Frontal Gyrus	6, 8, 9	1.4/na	3.6 (-3, 31, 40)/na
Middle Temporal Gyrus	21, 39	2.4/na	3.0 (-62, -41, -3)/na
Postcentral Gyrus	5, 40	0.2/na	2.9 (-53, -33, 49)/na
Supramarginal Gyrus	40	1.0/na	2.7 (-50, -57, 33)/na
Cingulate Gyrus	31	0.5/na	2.6 (0, -30, 35)/na
Inferior Temporal Gyrus	21	0.1/na	2.1 (-56, -56, -5)/na

Table 9. Anatomical description of the right executive control network. Voxels above the threshold of Z > 2 within converted Z map of each component are presented. Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html). na: no strong (Z > 2) contribution of the component.

Right Executive Control Network			
Area	Brodmann Area	volume (cc) left / right hemispheres	random effects: Max Value (x, y, z) left / right hemispheres
Inferior Parietal Lobule	7, 39, 40	2.6/13.6	3.4 (-45, -53, 52)/9.2 (48, -47, 52)
Superior Parietal Lobule	7	0.3/1.5	2.9 (-42, -59, 50)/7.4 (42, -59, 50)
Superior Frontal Gyrus	6, 8, 9, 10, 11	na/12.2	na/6.0 (36, 58, -5)
Middle Frontal Gyrus	6, 8, 9, 10, 11, 46, 47	0.1/25.1	2.0 (-42, 47, -2)/5.8 (33, 58, -8)
Inferior Frontal Gyrus	9, 10, 45, 46, 47	0.1/2.3	2.1 (-42, 50, 0)/5.2 (42, 55, 0)
Postcentral Gyrus	2, 5, 40	na/1.2	na/5.1 (56, -35, 49)
Supramarginal Gyrus	40	na/5.1	na/5.0 (56, -45, 35)
Angular Gyrus	39	na/1.1	na/4.2 (50, -56, 36)
Precentral Gyrus	9	na/0.4	na/3.8 (45, 25, 35)
Medial Frontal Gyrus	6, 8, 9, 10	na/2.6	na/3.7 (3, 34, 37)
Sub-Gyral	*	na/0.4	na/3.5 (42, 47, 3)
Precuneus	7, 19, 39	na/1.2	na/2.8 (42, -71, 39)
Middle Temporal Gyrus	21	na/2.9	na/2.8 (62, -35, -3)
Cingulate Gyrus	23, 31, 32	na/1.2	na/2.6 (3, 36, 29)
Superior Temporal Gyrus	22, 38	na/0.1	na/2.5 (53, -57, 28)
Paracentral Lobule	31	na/0.2	na/2.3 (3, -27, 43)

Table 10. Anatomical description of the auditory network. Voxels above the threshold of Z > 2 within converted Z map of each component are presented. Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html). na: no strong (Z > 2) contribution of the component.

Auditory Network			
Area	Brodmann Area	volume (cc) left / right hemispheres	random effects: Max Value (x, y, z) left / right hemispheres
Superior Temporal Gyrus	13, 21, 22, 38, 41, 42	20.5/22.5	7.3 (-62, -17, 9)/7.2 (62, -14, 9)
Transverse Temporal Gyrus	41, 42	1.5/1.4	6.6 (-59, -17, 12)/7.3 (62, -17, 12)
Postcentral Gyrus	1, 2, 3, 40, 43	3.5/4.7	6.2 (-62, -23, 15)/6.8 (62, -20, 15)
Middle Temporal Gyrus	21, 22, 39	1.3/2.3	6.5 (-59, 0, -3)/4.3 (62, 0, -5)
Precentral Gyrus	6, 13, 43	1.0/1.9	4.2 (-50, -14, 12)/5.1 (56, -11, 12)
Sub-Gyral	21	2.2/2.2	4.4 (-42, -1, -10)/3.8 (42, -1, -10)
Inferior Frontal Gyrus	47	0.5/1.4	3.1 (-39, 11, -13)/4.3 (56, 17, -6)
Insula	13, 22	6.5/5.8	4.1 (-45, -6, -2)/4.0 (50, -25, 15)
Extra-Nuclear	13	0.5/0.5	3.3 (-39, 2, -10)/3.4 (42, 5, -8)
Inferior Parietal Lobule	40	0.7/2.5	2.5 (-56, -31, 24)/3.4 (59, -25, 23)
Cingulate Gyrus	31	0.1/0.3	2.4 (0, 13, 32)/2.1 (3, 16, 30)
Uncus	28	0.1/0.1	2.3 (-33, 2, -20)/2.2 (30, 5, -20)
Anterior Cingulate	24, 32	0.1/na	2.1 (0, 27, 21)/na

Table 11. Anatomical description of the salience network. Voxels above the threshold of Z > 2 within converted Z map of each component are presented. Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html). na: no strong (Z > 2) contribution of the component.

Salience Network			
Area	Brodmann Area	volume (cc) left / right hemispheres	random effects: Max Value (x, y, z) left / right hemispheres
Superior Temporal Gyrus	22, 38	2.5/1.9	6.0 (-50, 14, -8)/4.8 (50, 17, -8)
Cingulate Gyrus	24, 32	3.7/4.4	5.7 (0, 25, 32)/5.4 (3, 22, 38)
Inferior Frontal Gyrus	45, 47	3.0/1.9	5.2 (-48, 14, -6)/4.2 (53, 17, -6)
Superior Frontal Gyrus	6, 8, 9, 10	11.8/10.6	5.1 (0, 14, 49)/5.1 (3, 18, 60)
Medial Frontal Gyrus	6, 8, 9, 32	2.2/2.6	4.7 (0, 11, 46)/5.1 (3, 17, 43)
Middle Frontal Gyrus	6, 9, 10, 46	10.7/6.7	4.6 (-30, 53, 19)/4.1 (30, 56, 19)
Anterior Cingulate	24, 32, 33	1.5/1.2	4.1 (0, 30, 21)/4.1 (3, 30, 23)
Insula	13, 47	2.3/1.0	3.6 (-42, 11, -3)/2.7 (42, 11, -6)
Sub-Gyral	*	0.4/0.1	3.4 (-42, 11, -8)/2.8 (45, 11, -8)
Superior Parietal Lobule	7	0.4/0.1	3.0 (-6, -64, 56)/2.3 (6, -64, 56)
Precuneus	7	1.3/1.0	3.0 (-3, -58, 58)/2.8 (3, -55, 58)
Extra-Nuclear	13, 47	0.2/na	2.4 (-33, 23, -1)/na
Precentral Gyrus	6	0.2/0.1	2.3 (-45, 2, 47)/2.2 (48, 2, 47)
Inferior Parietal Lobule	40	na/0.4	na/2.1 (59, -36, 29)

Figures

Figure 1. Estimated sources corresponding to centrotypes of clusters. Robust clusters are presented in quality rank order estimated from centrotypes of source signals.

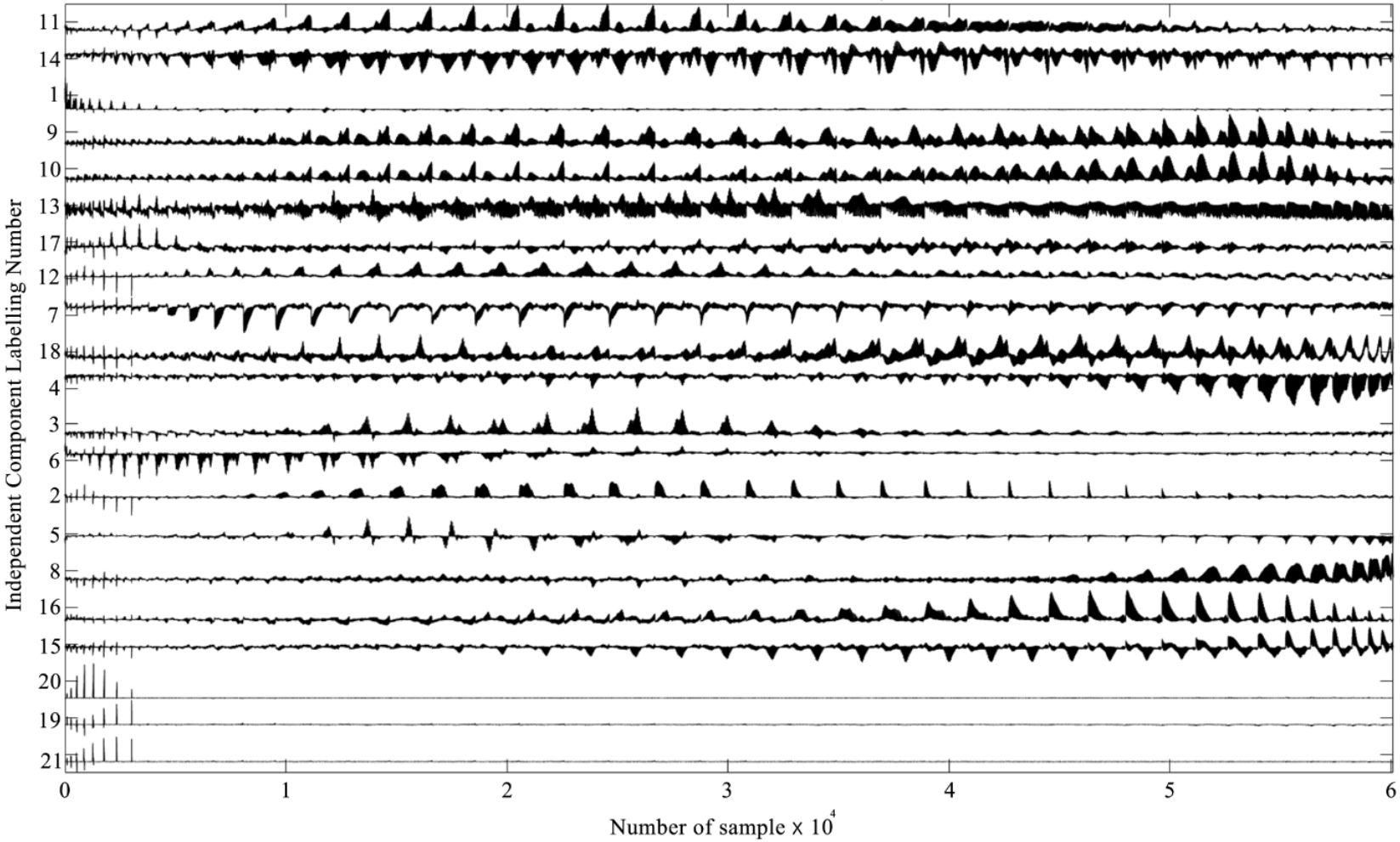
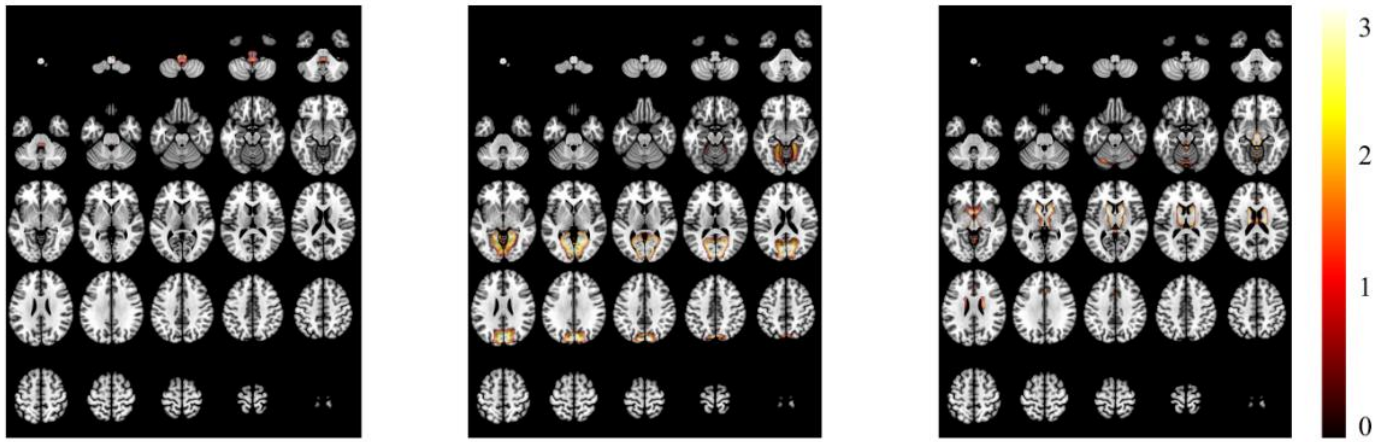


Figure 2. Functional networks identified by group ICA and overlaid on a standard image template. Z-scores are threshold at Z > 2.

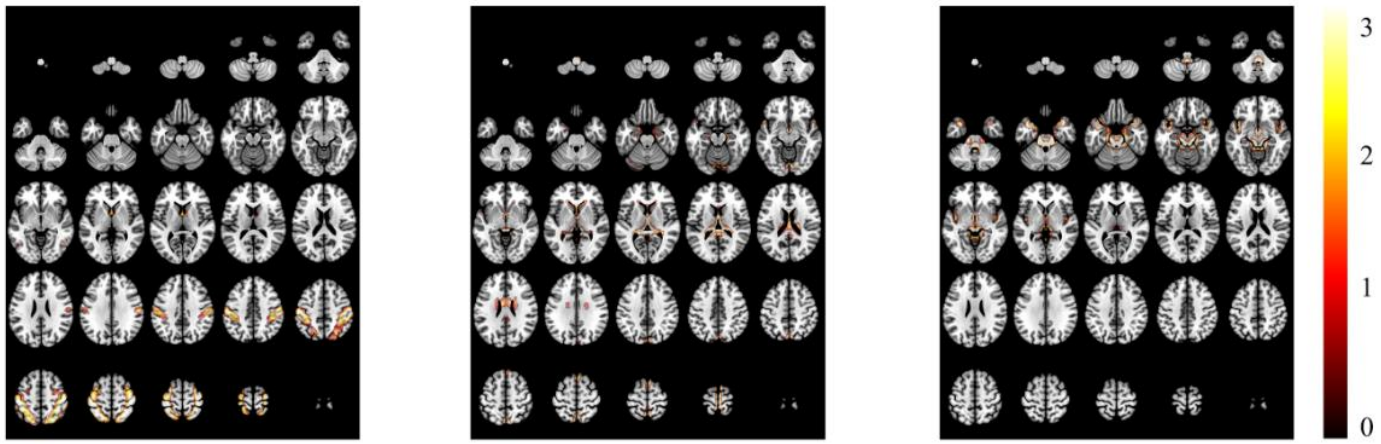


IC #1
Artifacts

IC #2
Visual Networks

IC #3
Basal Ganglia Networks

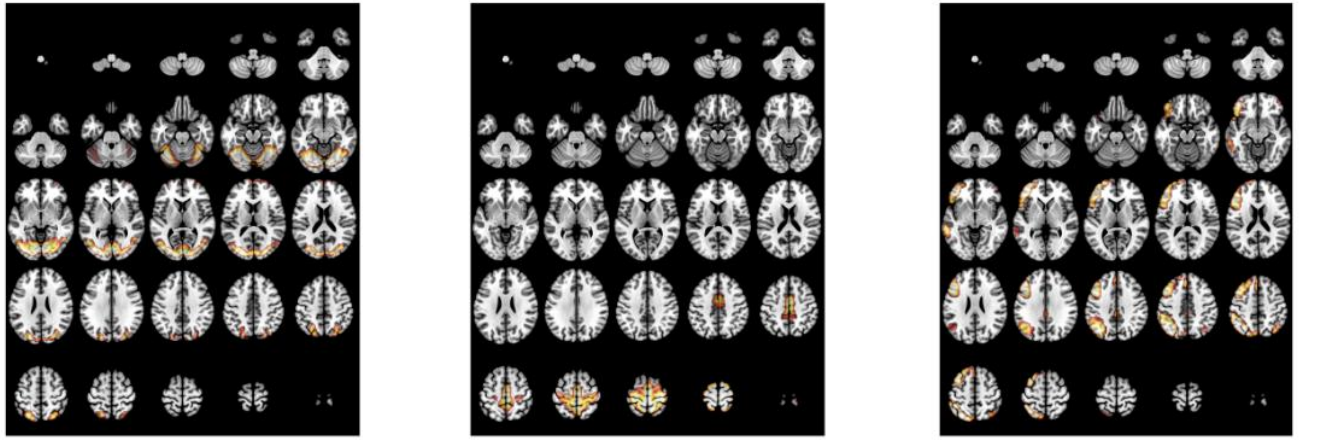
Figure 2. (continued)



IC #4
Sensorimotor Network

IC #5
Artifacts

IC #6
Artifacts

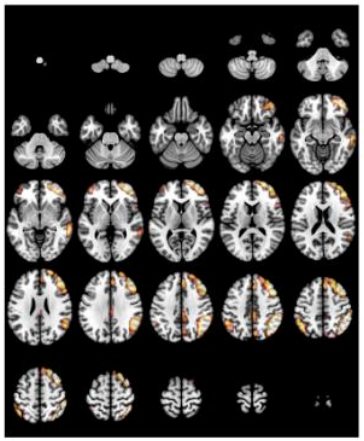


IC #7
Visual Networks

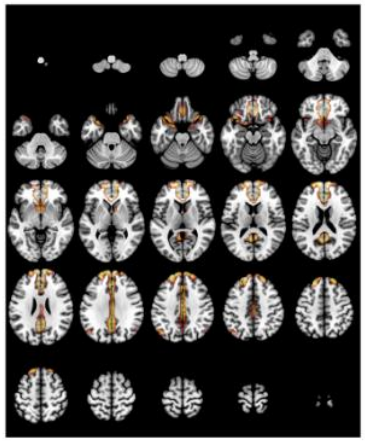
IC #8
Dorsal Attention Networks

IC #9
Left Executive Control Networks

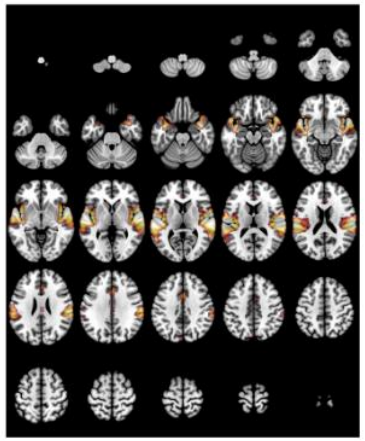
Figure 2. (continued)



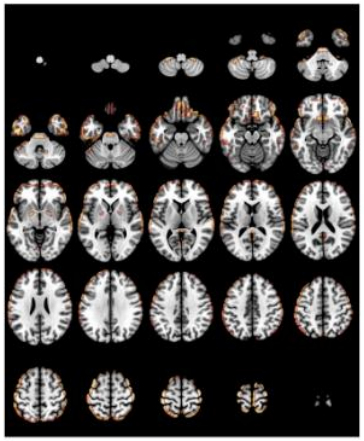
IC #10
Right Executive Control Networks



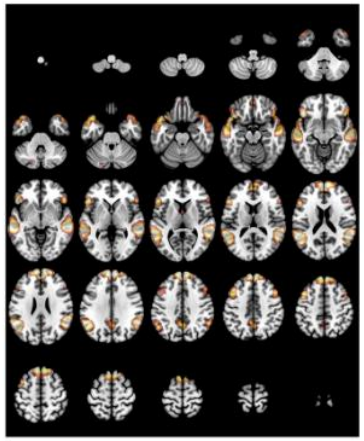
IC #11
Anterior Default Mode Networks



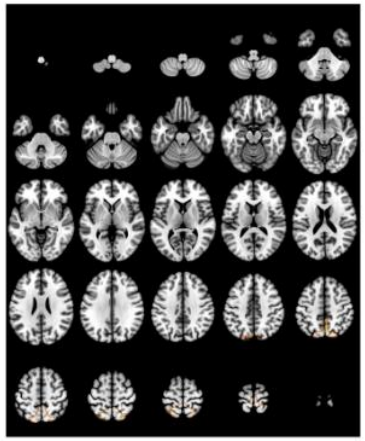
IC #12
Auditory Networks



IC #13
Artifacts

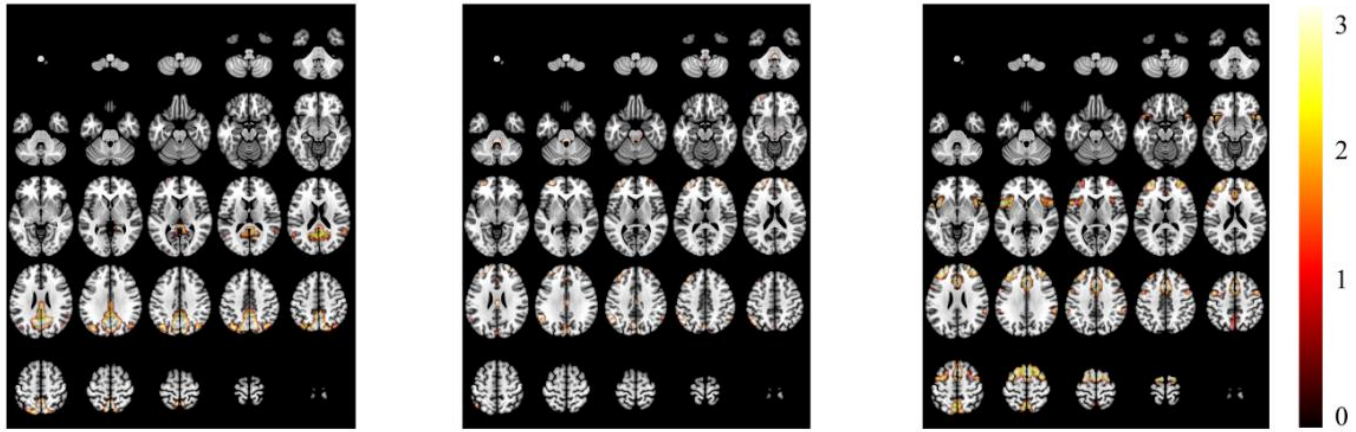


IC #14
Language Networks



IC #15
Artifacts

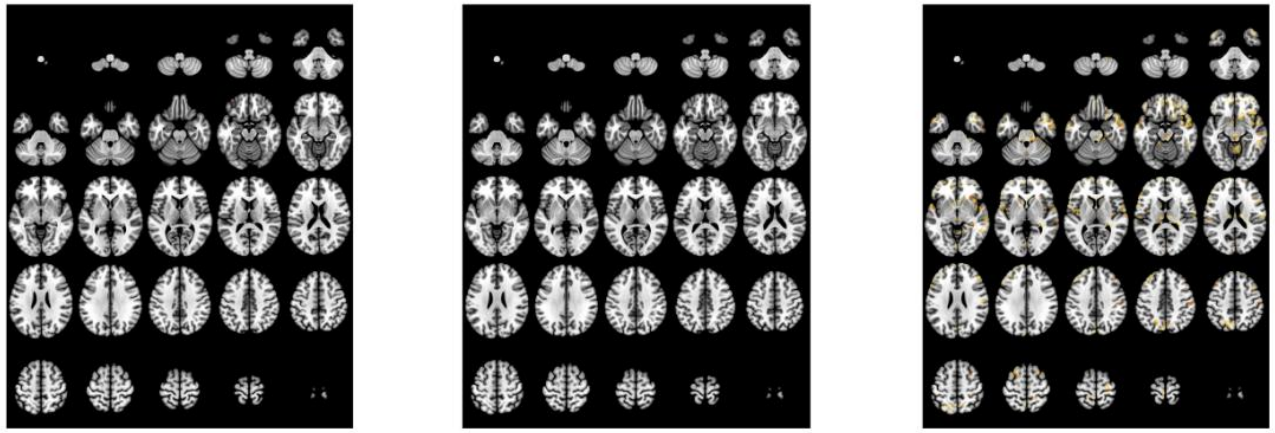
Figure 2. (continued)



IC #16
Posterior Default Mode Networks

IC #17
Artifacts

IC #18
Salience Networks



IC #19
Artifacts

IC #20
Artifacts

IC #21
Artifacts

Figure 3.The functional networks of present study (in green) and the corresponding functional networks from atlases[41, 112, 113] (in red). Overlapping regions are depicted in yellow.

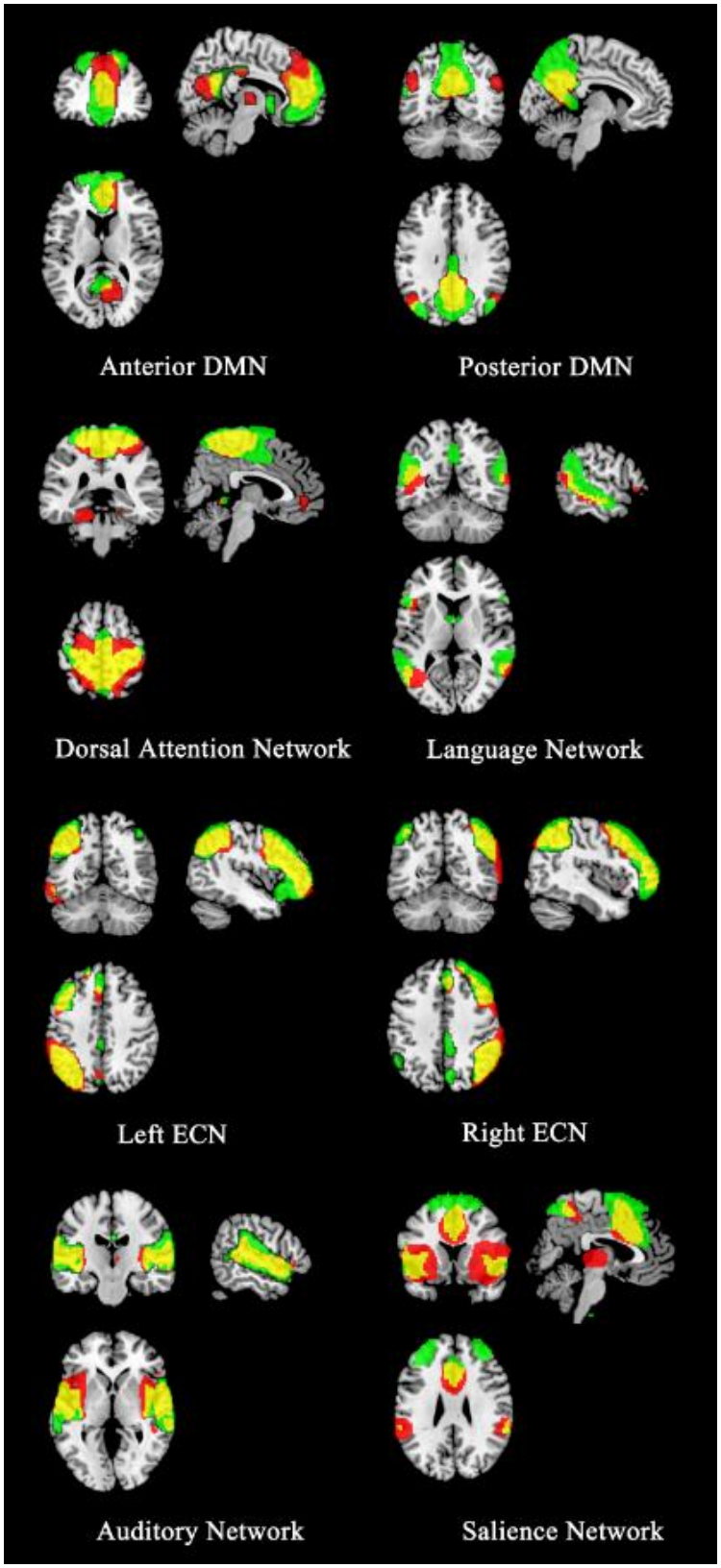


Figure 4. The interaction between functional networks. Significantly altered functional network interactions are indicated by red line at the significance level of $p < (0.05 / 28)$. Anterior default mode network: A.DMN; salience network: SN; right executive control networks: R.ECN; dorsal attention network: DN; posterior default mode network: P.DMN; auditory network: AN; left executive control networks: L.ECN; and language network: LN.

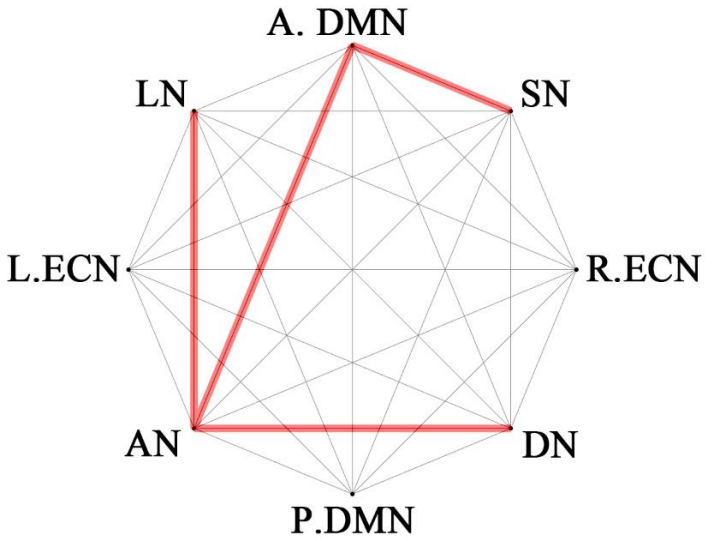


Figure 5. Mean correlation coefficients of significantly altered functional network connectivity. Interaction between (A) anterior default mode network (DMN)

and salience network; (B) language network (LN) and auditory network (AN); (C) anterior DMN and AN; (D) dorsal attention network and AN; All values were Z-transformed. *Group that shows significantly different functional network connectivity compared to healthy control group. ◇Group that shows significantly different functional network connectivity compared to schizophrenia patient group. FEP: first-episode psychosis; CHR-C: CHR subsequently converted to full-blown psychosis; CHR-NC: CHR who did not convert to full-blown psychosis; and HC: healthy control.

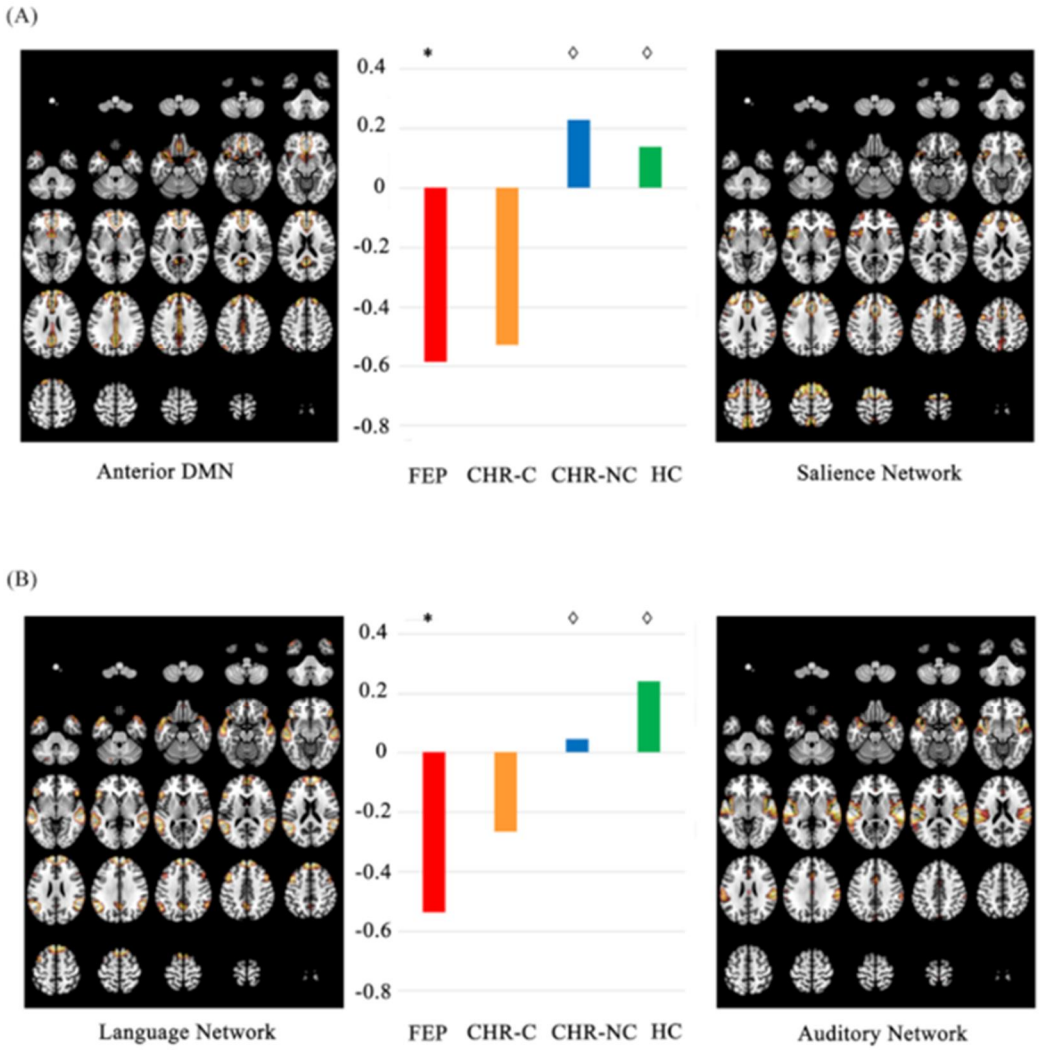
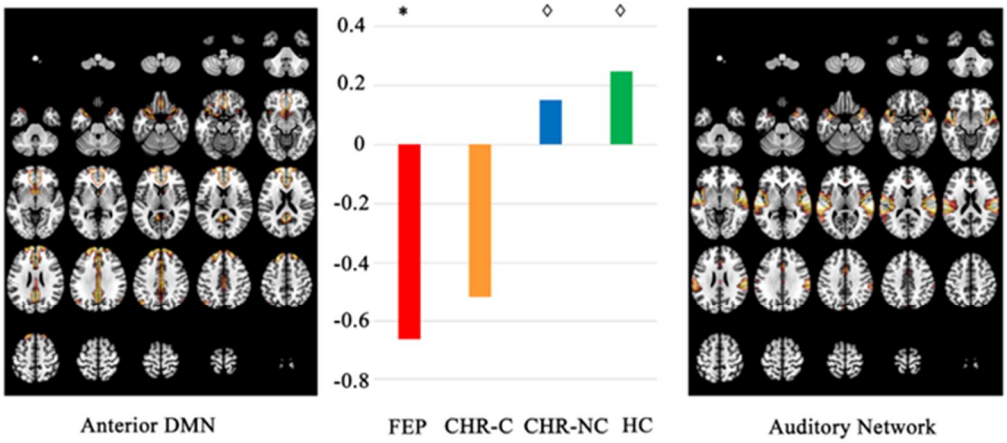


Figure 5. (continued)

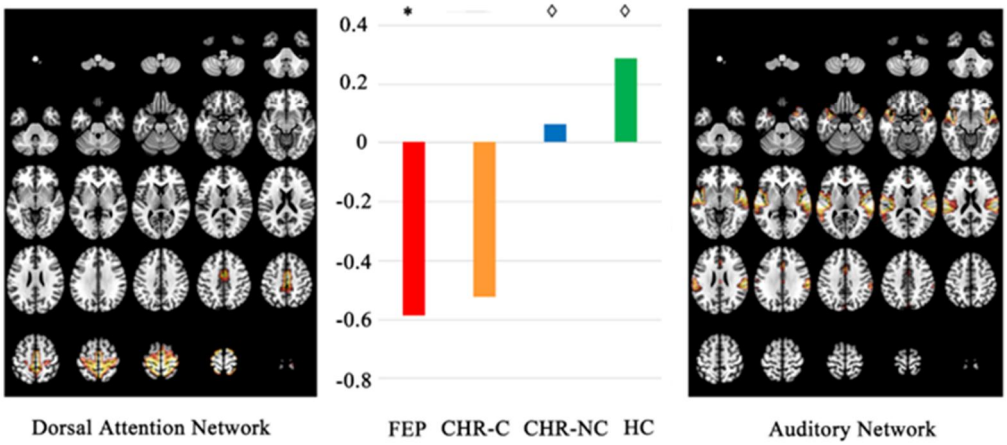
(C)



Anterior DMN

Auditory Network

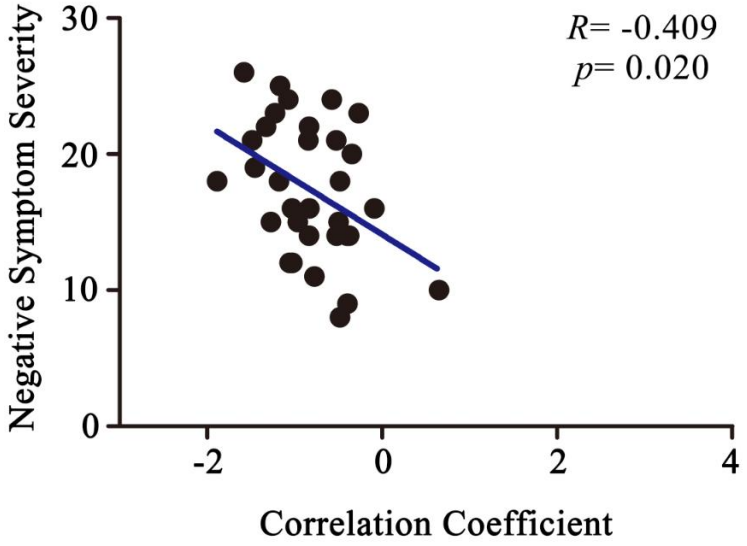
(D)



Dorsal Attention Network

Auditory Network

Figure 6. Association between functional network connectivity and psychotic symptom severity in the FEP group. The correlation coefficients (Fisher's Z-transformed) of the functional network connectivity between anterior default mode network and salience network and the overall negative symptom severity assessed with the Positive and Negative Syndrome Scale[107] were significantly correlated.



Abstract in Korean

정신증 고위험군은 조현병 전구기 증상을 보이는 사람이고, 실제 이 중 일부는 조현병이 발병한다. 정신증 고위험군 중 어떤 사람들이 조현병이 발병하는지 뇌의 구조를 통해서 예측하려는 시도들이 있었고 뇌 전두엽 및 측두엽의 구조 이상이 예측 마커로 사용될 수 있다는 보고가 있었다. 하지만 연결성 이상으로 야기되는 조현병을 뇌의 네트워크 단위에서 연결성을 통해서 예측 마커를 찾으려는 시도는 아직 없었다.

조현병의 발병 마커를 네트워크 차원에서 찾기 위해 최소 12 개월동안 종단 연구를 진행하였다. 종단 연구 시작점에서 초발 정신병 환자군 35 명, 정신증 고위험군 69 명, 그리고 정상 대조군 90 명의 휴지기 기능 자기공명영상을 획득하였다. 8 개의 휴지기 기능 네트워크를 추출하였고, 이들 간 총 28 개의 가능한 짝들에서 군 간 차이를 보이는 조합들을 찾았고, 이들과 정신증 증상 심각도의 상관관계를 분석하였다.

69 명의 정신증 고위험군 중 10%, 즉 7 명이 실제 조현병이 발병하였다. 초발 정신병 환자군, 정신증이 발병한 정신증 고위험군, 정신증이 발병하지 않은 정신증 고위험군, 정상 대조군에서 나이, 성별, 손잡이 여부에는 차이가 없었다. 총 28 개의 가능한 조합들 중에 4 개의 조합에서 군 간 유의한 차이를 보였다. 모든 조합들에서 초발 정신병 환자군은 정상 대조군에 비해 기능적 네트워크 간 연결성의 가장 큰 감소를 보였다. 정신증이 발병한

정신증 고위험군은 초발 정신병 환자군와 기능적 네트워크 간 연결성에서 유의한 차이를 보이지 않은 반면, 정신증이 발병하지 않은 정신증 고위험군은 초발 정신병 환자군에 비해 유의하게 큰 기능적 네트워크 간 연결성이 관찰되었다. 초발 정신병 환자군에서 손상을 보인 앞쪽 디폴트 모드 네트워크와 현출성 네트워크 간 연결성은 이 군에서 보이는 음성 증상의 심각도와 관련있는 것으로 나타났다.

본 연구는 기능적 네트워크의 연결성이 추후 정신증이 발병 또는 발병하지 않은 정신증 고위험군에서 차이를 보일 수 있음을 증명하였다. 더 나아가 본 연구 결과는 전구 증상에서 유의한 차이를 보이지 않는 두 군간 추후 정신증 발병의 조기 진단 마커를 찾는데 기능적 네트워크의 연결성의 활용이 중요한 단서를 제공할 수 있음을 시사한다.